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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

BERCH, MARK L

ART UNIT

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MAIL DATE

DELIVERY MODE

03/17/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/533,183	Applicant(s) NISHINO ET AL.	
	Examiner /Mark L. Berch/	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01/07/2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-4 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 2 is/are rejected.
- 7) ☒ Claim(s) 3 and 4 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5414081 alone, or alternatively Sakurai or US 5414081 in view of EP 188816 or US 5578722.

In Sakurai, see the conversion of 18 to 19 in scheme 4. This corresponds to the claimed reaction, in which R₂ is t-butyl; diisopropylethylamine was used as base. The sole difference is that the claims call for the trimethylsilyl protecting group, and the prior art has the t-butyldimethylsilyl protecting group. This is a very small difference; both are trialkylsilyl protecting group, and are protecting an OH group at a remote point – i.e. not at the reacting site.

Similarly, in US 5414081, see step (4) of example 6, which basically has the same teaching, albeit with a different thiol being reacted.

First, US 5414081 teaches that the protecting group can be triloweralkylsilyl, see column 2, lines 59-60. Since trimethylsilyl is the simplest triloweralkylsilyl, that would be understood by one of ordinary skill in the art as an alternative to the t-butyldimethylsilyl used in the example. In addition, for the R₄=H option in the rejected claims, the definition

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of R1 in the reference includes the unprotected OH, i.e. it says that the OH “may be protected”. Thus, the reference alone renders obvious the use of the unprotected OH or the OH protected by trimethylsilyl.

In addition, the secondary references establish that the art considers the two to be alternatively useable in the reaction. In EP 188816, page 23 (IX) to (VII) shows the general reaction here. X' is taught as a protected OH group (page 14, lines 1-2). L is taught as the active ester of an OH group (page 21, lines 12-13), and specifically, the active ester of diphenylphosphoric acid, i.e. the exact one used here is taught at 10th and 9th from last line of page 21. Page 3, lines 9-10 teaches exactly two choices for silyl protecting groups, viz, the trimethylsilyl protecting group of the claims, and the t-butyldimethylsilyl of the primary references, establishing the two as equivalent. Indeed, example 13 shows the use of the trimethylsilyl protecting group. The exact details are not given at that point, but the example refers to example 11-3, which in fact has the t-butyldimethylsilyl group, against emphasizing the fact that these are alternatively used. Example 11-3 is applicant same overall process. The cyclization, and phosphorylation correspond to what appears in this specification, page 21, second step. Indeed, the reagent used in example 11-3, diphenylchlorophosphate, and used by applicants in reference example 3, is the same, albeit the compound is named differently. This is then reacted with the thiol, as seen on page E-58 of the reference.

In addition, the reference clearly teaches that the displacement with the thiol can be done with the OH unprotected (note that R4 in claim 1 can be H). See page E-51.

A similar teaching appears in 5578722, this time for the triethylsilyl group. The overall reaction is seen in column 48, IV to III to V. X is a protected OH group, and three

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trialkyl silyl groups are named at column 3, lines 5-7: trimethylsilyl group, triethylsilyl group, and t-butyldimethylsilyl group. This again establishes that these are considered alternatively useable. L is again taught as the active ester of an OH group and specifically, the active ester of diphenylphosphoric acid (column 5 line 7). The use of the triethylsilyl group is seen in example 7.

Thus, in this circumstance, applicants have substituted one known element (a protecting group) for another of the same function. This element, and its function have thus been shown to be known in the art. One of ordinary skill in the art could have substituted one known element for another, and the results would have been predictable, as that is precisely the teaching of the secondary reference. There is a reasonable expectation of success, since success was indeed achieved with the alternative element (the trimethylsilyl protecting group) in the secondary references. Note *In re Fout*, 213 USPQ 532; *In re O'Farrell*, 7 USPQ2d 1673, *KSR International Co. v. TeleflexInc.*, 82 USPQ2d 1385.

The traverse is unpersuasive. Applicants first argue that that the TBS protecting group requires the use of fluoride reagents which are "expensive" and cause problems in "production facilities" or strong acids which "causes yield loss". However:

a) Even if true, these are all expected differences; one knows these things. Expected differences are not evidence of unobviousness, *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967); *Ex parte Blanc*, 13 USPQ2d 1383; *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

b) There are in fact a wide variety of methods for removing the TBS group; this is a well developed art. To rebut applicants arguments, there is cited the Greene reference which discloses a very wide variety of techniques available.

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Next, applicants argue that the cited references do not teach applicants' particular method for removing the TMS or TES group. This is correct, but the claims as written do not require that step.

In the paragraph bridging pages 6-7 applicants in effect argue that the process is not novel, which is agreed with, but the rejection is for obviousness.

Applicants next argue that TMS is one of many protecting groups taught by EP 188816. This is correct, but the examiners point is that in the category of the silyls, exactly two are mentioned: these two. That suggests that these two are considered alternatively useable for the invention. Not that they are identical --- no two protecting groups have the exact same properties, but rather, that each is considered useable at that position.

Applicants then point out that in example 13 of EP 188816, the PNZ group was used for the carboxyl. This is correct, but example 13 is not being used as a primary reference; example 13 does not itself render the process obvious. Example 13 was pointed to as evidence that TMS was not only listed as an alternative to the TBS group, it was actually employed in an example. An example in a secondary reference always has some difference --- otherwise, example 13 would itself anticipate.

In addition, the reference clearly teaches that the displacement with the thiol can be done with the OH unprotected (note that R4 in claim 1 can be H). See page E-51.

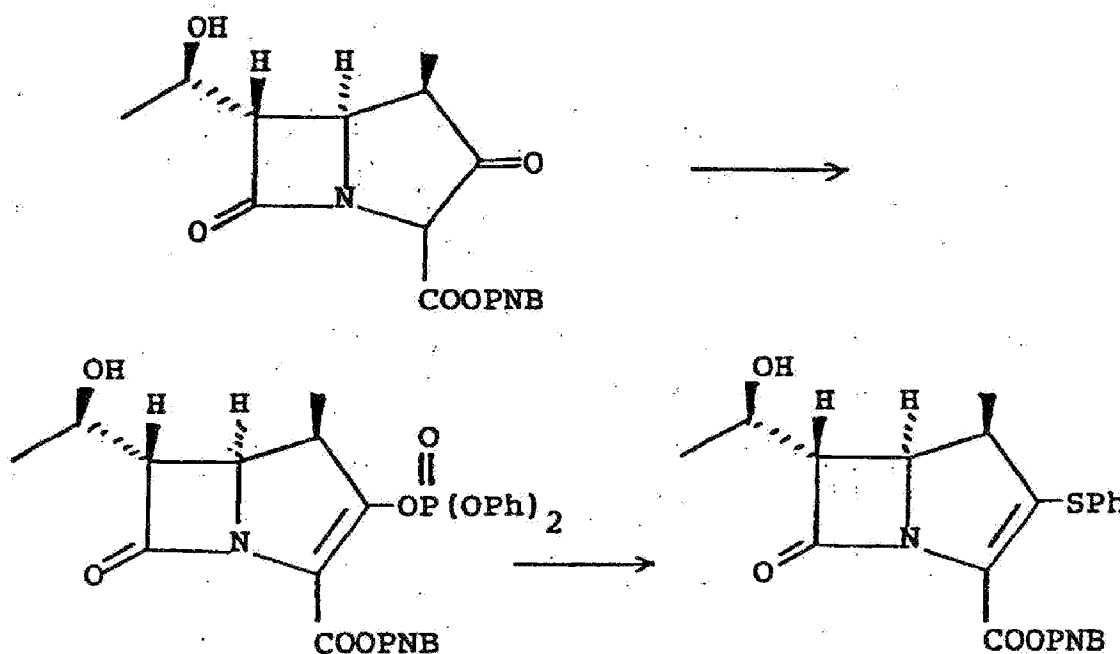
Finally, applicants argue that "But it is impossible to obtain a compound (2) having H as R4 from the compound of example 17, because TBS groups is deprotected by using a fluorine compound, reacting in a strong acid aqueous solution, or reacting in a weak acid aqueous solution for long hours and such ways promote decomposition of an

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alkanoyloxymethyl moiety of carboxylate residue, phosphoric ester moiety and five membered ring structure...". However:

1) even if applicants' argument were entirely persuasive, the rejection would still be sound, because this is an alternative argument, based on $R_4=H$. No claim requires $R_4=H$. This aspect deals with the situation where $R_1=R_4=H$.

2) This somewhat misses the point of the teaching of the reference. First, the actual text:



This teaches one of ordinary skill in the art that the displacement, converting the $=O$ to $-SPh$ can in fact be done with the hydroxy group as unprotected. The particular reaction used a different carboxy protecting group. This is true, but that simply means that the reaction is not an anticipation. The same is true for applicants' "In fact, there is no example of a compound (2) having H as R_4 in the references shown in the Office Action" --- if there were, the secondary reference might well anticipate. Moreover, the examiner is not

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saying that this reaction --- which is in the secondary reference – itself makes claim 1 obvious. The point here is that one of ordinary skill in the art, in modifying the primary reference, knows not only that one can use the TMS or TES as an alternative to the TBS as OH-protecting group, but as an alternative, also knows for, the above reaction that one can use the unprotected OH as an alternative to the OH protected by TBS.

Claim Objections

Claims 3-4 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to /Mark L. Berch/ whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark L. Berch/
Primary Examiner
Art Unit 1624

3/19/2008